PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 921 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/003144	International filing date *(day/month/year)* 24.03.2005	Priority date *(day/month/year)* 24.03.2004
International Patent Classification (IPC) or national classification and IPC A61K31/47, C07D207/48, C07D215/26, C07D215/60		
Applicant CHIESI FARMACEUTICI S.P.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.01.2006	02.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Härtinger, S Telephone No. +49 89 2399-8289

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/003144

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-7 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/003144

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-6
	No:	Claims	1-4
Inventive step (IS)	Yes:	Claims	5-6
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re item I:

1. The amended set of claims filed with the demand for international preliminary examination do not go beyond the disclosure in the international application as filed, because new claim 1 is the result of the combination of previous claim 1 with claim 3 dependent thereon.

Re item V:

1. The invention relates to TA 2005 in an alleged new form with a particular crystalline degree of at least 90% (claims 1-4) and a process for the preparation the same (claims 5-6). In his letter of 24.01.06, the applicant acknowledged that "*[i]n fact, the experimental code TA 2005 is normally referred only to the form (R,R)*", which is also the enantiomerical form of the compounds in the present claims.

   The relevant prior art has been indicated in the search report.
   D1: US-A-4 579 854
   D2: KIKKAWA et.al., JAPANESE J. PHARMACOL., 57, 1991, 175-185
   D3: VOSS et.al., EUR. J. PHARMACOL., MOL. PHARMACOL., 227, 1992, 403-9
   D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HOSHIKO, KENICHIRO ET AL: "Treatment of inflammatory diseases with drugs containing carbostyril derivative" XP002334111 retrieved from STN Database accession no. 1997:769190
   D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IZEBOUD, C. A. ET AL: "Stereoselectivity at the .beta.2-adrenoceptor on macrophages is a major determinant of the anti-inflammatory effects of .beta.2-agonists" XP002334112 retrieved from STN Database accession no. 2000:627207
   D6: US-A-6 030 604

2. Process claims 5-6
   The subject-matter of claims 5 and 4 appears to have met all the requirements of Art. 33 PCT, because none of the documents discloses the present sequence of process steps. From the reading of the present application, it would appear that the technical

effect of reducing the volume of the TA 2005 solution prior to the addition of the diisopropyl ether above 30 °C is the increase of enantiomeric purity and crystallinity of TA 2005. Although D1 makes use of the same solvent system for recrystallizing TA 2005 (see example step 4(3-a)), no teaching as to the beneficial effect from the combination of the present process features can be derived from the prior art. Hence, the process as claimed solves in a not obvious manner the problem of providing a purification process of otherwise known TA 2005.

3. Product claims 1-4

Enantiomeric purity and the degree of crystallinity of TA 2005 are properties which are immediately linked by method used to synthesize and purify the compound. This becomes apparent to the person skilled in the art from the disclosed procedures in D1. Thus, the example 4 of D1 discloses the purification of TA 2005 by recrystallization from a mixture of ethanol, water and isopropyl ether. The terms "crystals", "crystallized" used in D1 together with the indication of the (R,R) form in the chemical name of the purification method leave no doubt that the product obtained in the prior art is a purified and crystalline form of TA 2005. The resultant 1R enantiomer has a melting range of 170-171.5 °C. The corresponding 1S enantiomer is recrystallized from a mixture of methanol and ether. The 1S form has a meting range of 166-167 °C, i.e. a range which is different from that of the 1R form. It is common general knowledge in the art that a mixture of products, each having a melting point which is different the other compound, will in general result in a melting range which is different from that of the individual compounds. The skilled person will therefore expect that a mixture of enantiomer of TA 2005 will also have a melting point (or melting range) which is different from that of the individual enantiomers.

It is noted that the presently claimed (R,R) form of crystalline TA 2005 has a melting range of 180-200 °C. This range differs from the narrower range explicitly disclosed in D1.

This authority is unable to acknowledge novelty of the presently claimed TA 2005 form on the mere basis of an differing melting range.

In his letter of 24.01.06, the applicant held that the present application "*does not*

concern the enatiomeric purity of the product per se, in that the object is an optically active compound in its form (R,R), but the enantiomer (R,R) in the solid state having distinctive characteristics described from page 7 lines 25 to page 8 line 16 of the application, in particular a crystalline degree of at least 90%".

This authority is of the opinion that all characteristics mentioned on pages 7 and 8 of the description relate to the level of purity of TA 2005, and based on common general knowledge, the purity of the product will influence both the value of the melting point and the crystallinity of the compound. In the light of the various enantiomers already made available to the public, it is clear that one factor, which may have an influence on the melting point of the product, is the enatiomeric purity.

In his letter of 24.01.06, the applicant alleged that "*conventional purification methods do not allow to achieve this result*", whereby the said result refers to the characteristics disclosed on pages 7 and 8 of the description.

This statement is silent about the purification methods and conditions used by the applicant. It is also not supported by factual evidence, for instance in the form of test protocols. As crystalline TA 2005 undisputably can be obtained with prior art methods, this authority cannot accept these allegation as a proof that all conventional purification methods (there are many more than just recrystallization) failed in the purification of TA 2005 so as to obtain crystals having the characteristics indicated in the present claims.

The difference in the level of purity, as derived from the distinct melting range of otherwise crystalline TA 2005 in D1, can therefore not be accepted as a novelty bringing feature. Since no evidence has been given in support of the alleged special case, D1 is considered to make available to the public the TA 2005 substance in all grades of purity. Sine enantiomeric purity and crystallinity are linked, the presently claimed form of TA 2005 as defined by the melting range, XRD peaks and degree of crystallinity is not considered to have met the novelty requirement of Art. 33(2) PCT.

b) D2-D5 report that TA 2005 had been obtained from different sources. For analogous reasons to that given above, any of these reports are considered to take

away the novelty of the claimed compounds. In this respect it is noted that the lack of novelty may be implicit in the sense that, in carrying out the teaching of the prior art documents, the skilled person would inevitably arrive at a TA 2005 compound with all features of the claim, irrespective of whether the crystallinity has been expressively mentioned or not.

c) The document D5 teaches that 1R and 1S enantiomers largely differ as to the quantitative efficiency of the drugs. D6 teaches, that dry powder formulations for the treatment of respiratory disorders may be produced from micronized TA 2005 particles in a finely divided form. Based on this combined teaching, the skilled person would have tried to produce the more active form in the highest achievable degree of purity. Hence, TA 2005 with a higher level of purity and crystallinity is considered to have obvious properties, which cannot serve as the basis for inventive activity. Any novel claims drawn to pure and crystalline TA 2005 appear therefore to solve in an obvious manner the problem of providing a further form of TA 2005. In the absence of not obvious properties of the compounds, i.e. use related properties other than just a different parameter value expressing the crystall form, habit or purity, the product claims 1-4 do not meet the requirements of Art. 33(3) PCT.

Re item VI:

1. The following documents have been published between the priority and filing date of the present application.

   D7: ROSSONI, GIUSEPPE ET AL: "Positive interaction of the .beta.2-agonist CHF 4226.01 with budesonide in the control of bronchoconstriction induced by acetaldehyde in the guinea-pigs" BRITISH JOURNAL OF PHARMACOLOGY , 144(3), 422-429 CODEN: BJPCBM; ISSN: 0007-1188, 10 January 2005 (2005-01-10), XP002334110

   D8: WO 2005/013945 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 17 February 2005 (2005-02-17)

2. The products CHF 4226 and TA 2005 disclosed therein do not form part of the state

of the art as defined in the PCT. D7 and D8 have therefore not been considered further in this report.

Re item VIII:

1. The process claim 6 lacks clarity in the meaning of Art. 6 PCT, because technical feature, which have been presented in the description as a "critical feature" to achieve the allegedly novel form of TA 2005, are missing in the claim (see the ratio for ethanol:water and the temperature in the precipitation step).

CLAIMS

1. 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride characterized by a melting range of 180-200°C determined by Differential Scanning Calorimetry, a X-ray powder diffraction pattern having inter alia one or more of the following characteristic peaks: 12.2; 13.6; 16.3; 18.0; 18.2; 19.2; 21.4; 21.9; 22.8; 23.5; 24.2; 24.9; 26.6; 28.5; 29.4; 29.9; and 33.9 ± 0.2 degrees /2 theta **and a crystalline degree expressed as weight % of the crystalline compound with respect to the total weight of the compound of at least 90%.**

2. 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino] ethyl]-2(1H)-quinolinone monohydrochloride of claim 1 characterized by a melting range of 185-195°C determined by Differential Scanning Calorimetry.

3. 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride of claims **1 or 2** having a crystalline degree expressed as weight % of the crystalline compound with respect to the total weight of the compound of at least 93%.

4. 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride of **any** claims from 1 **to 3** having a crystalline degree expressed as weight % of the crystalline compound with respect to the total weight of the compound of at least 95%.

5. A process for the preparation of a compound as claimed in **any** claims **from** 1 **to 4** comprising crystallising or re-crystallising the compound from an aqueous ethanol solution added with diisopropyl ether wherein the aqueous ethanol solution is concentrated to a volume comprised between 1/2 and 1/3 of

the initial volume and the addition of the diisopropyl ether is performed in at least 5 minutes.

6. A process according to claim **5** further comprising the step of re-crystallization from a protic solvent comprising ethanol, isopropanol or their aqueous mixtures.